

Measuring isomers and polymorphs

Featuring the Nicolet Summit X FTIR Spectrometer

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Figure 1. Nicolet Summit X FTIR Spectrometer with Everest Diamond ATR Accessory, powered by OMNIC Paradigm Software.

Introduction

Isomers and polymorphs are of great interest to pharmaceutical labs due to the highly variable chemical properties they can exhibit. Isomers are molecules that share the same chemical formula but differ in the structural arrangement of atoms, resulting in different chemical properties. Polymorphs also share the same chemical formula but differ in their lattice arrangement. These different crystal forms also result in different chemical behavior.

Vibrational spectroscopy is a popular identification techniques for a wide range of organic and inorganic chemistries, as molecular vibrations are sensitive to differences in local environments, structures, and solvents. Fourier transform infrared spectroscopy (FTIR) is a simple, non-destructive, and well-established vibrational-spectroscopy technique for the identification of isomeric chemistries. Raman spectroscopy, meanwhile, is considered to be an effective tool for the study of polymorphs, as it is highly sensitive to changes in molecular backbone bonds.

In this study, FTIR spectroscopy is used to study simple molecules such as acetamidophenol and its isomers as well as polymorphic forms of acetaminophen, a common analgesic and antipyretic used in many over-the-counter and prescription formulations. It is well characterized for its pharmacological properties and structure, making it an ideal test molecule.

Materials and methods

All materials used in this analysis were purchased from Sigma Aldrich.

FTIR analysis

FTIR spectra were collected on a Thermo Scientific™ Nicolet™ Summit™ X FTIR Spectrometer equipped with a deuterated triglycine sulfate (DTGS) detector. In each experiment a small amount of sample was placed on a Thermo Scientific™ Everest™ Diamond Attenuated Total Reflection (ATR) Accessory. Thermo Scientific™ OMNIC™ Paradigm Software was used for measurement and data analysis. Figure 1 shows the complete setup of the instrument, including the Everest ATR Accessory and laptop running OMNIC Paradigm Software.

Identifying isomers

Three isomeric forms of acetaminophen were analyzed. Figure 2 shows their spectra and corresponding chemical structures. Close observation of the fingerprint region from 500–1500 cm^{-1} shows that while there are similar peaks in all three spectra, there are also drastically different peaks that can be used to identify and characterize these molecules. Each spectrum was acquired in seconds using the Everest Diamond ATR Accessory with only a tiny amount of sample, making this analysis ideally suited for the QA/QC of raw materials as well as end products.

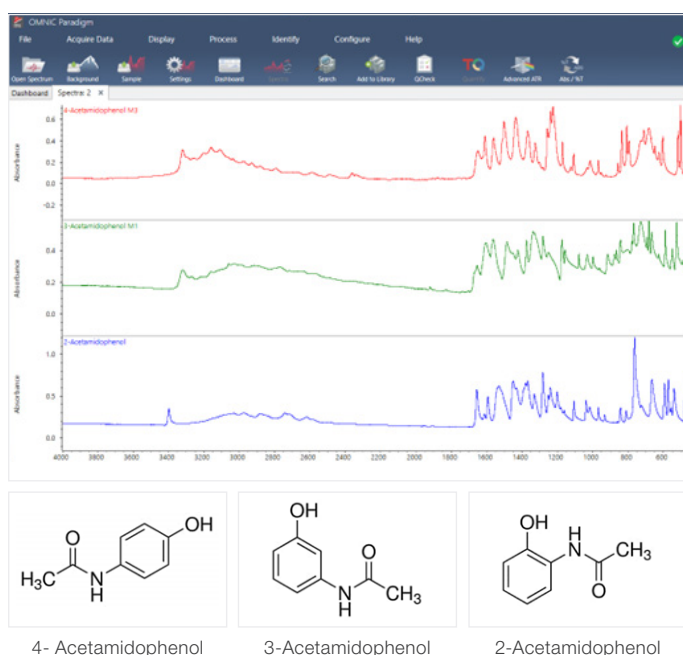


Figure 2. OMNIC Paradigm Software screen capture showing different isomeric forms of acetaminophen.

Identifying polymorphs

Although they consist of the same compound, polymorphs are known to crystallize into a variety of morphologies under differing physical conditions. The efficacy of pharmaceutical drugs depends strongly on their polymorphic form, making this a crucial aspect of NDA and patent application processes. In this study, a drop of acetaminophen was dissolved in ethanol and placed onto the Everest ATR Accessory. Time-based data collection with OMNIC Paradigm Software monitored the spectra as the ethanol evaporated. Initial spectra were dominated by the peaks of the ethanol solvent. After approximately 10 minutes of drying, the spectrum of dry acetaminophen was observed. Subsequently, the spectrum changed over the span of several minutes into a second form that then remained stable (Figure 3). This is due to a change in morphology caused by the drying process. Figure 3 shows the OMNIC Paradigm Software time-analysis window; the profile for each of the polymorphs observed in this study are shown on top, using characteristic peaks at 800, 1042, and 1500 cm^{-1} . The data indicates an increase in the peak intensity and stabilization for each of the polymorphic forms. The spectrum connected to polymorph ph1042 is shown at the bottom of Figure 3.



Figure 3. Time evolution of various peaks in the acetaminophen spectrum upon drying.

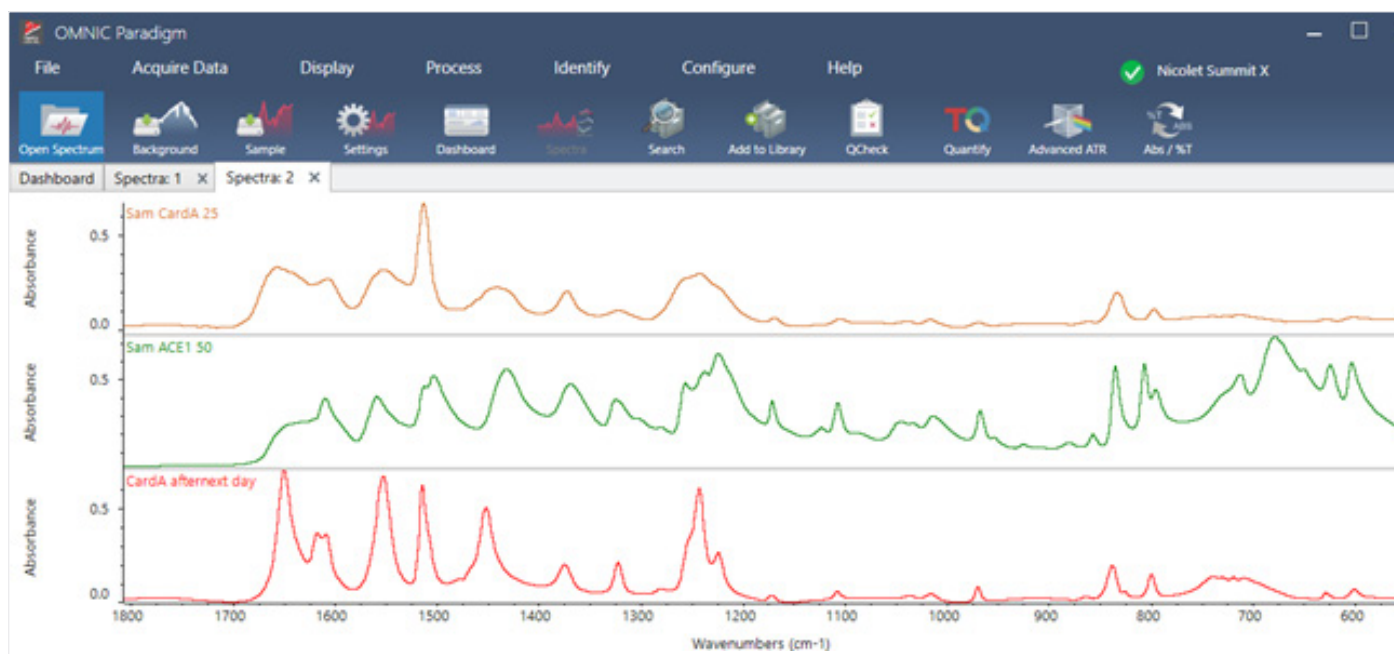


Figure 4. Fingerprint region spectra for three “terminal” polymorphs from acetaminophen, produced at a variety of different conditions. Spectrum A corresponds to amorphous acetaminophen, Spectrum B is the monoclinic form, and Spectrum C is the orthorhombic form.

It is an established phenomenon that the same molecule can crystallize in slightly different ways on different matrices. In order to look into this effect further, a second variant was tested using an infrared window. Acetaminophen was deposited onto an infrared transparent polyethylene membrane; drying was monitored using transmission spectroscopy. After several minutes, the spectrum stabilized with a different profile as compared to either of the diamond ATR measurements. Figure 4 shows the results of all three experiments (short time ATR, long time ATR, and transmission).

Search results and published literature suggests that Figure 4, Spectrum A corresponds to the amorphous form of acetaminophen, Spectrum B is the monoclinic polymorph (Form 1) and Spectrum C is the orthorhombic polymorph (Form 2). It is beyond the scope of this study to fully investigate the development of a different polymorph on the hydrophobic micro-porous membrane, however, the sensitivity of infrared to this morphology is evidently quite dramatic.

Conclusions

In this application note, we have demonstrated that the high performance of the Nicolet Summit X Spectrometer, combined with the rapid analysis of the Everest Diamond ATR Accessory, provides a powerful tool for rapidly screening, classifying, and analyzing isomers and polymorphs of active pharmaceutical ingredients such as acetaminophen.

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